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Scientists Identify an Inherited Gene That Strongly Affects Risk for the Most Common Form of Melanoma

Researchers at the National Cancer Institute (NCI), part of the National Institutes of Health, have identified a link between inherited and acquired genetic factors that dramatically increase the chance of developing a very common type of melanoma. This finding appears in an online version of *Science** on June 29, 2006, and was a collaborative effort led by scientists at NCI and the University of California San Francisco. Also involved in the study were researchers at the University of Pennsylvania, Philadelphia, and Bufalini Hospital in Cesena, Italy**.

"Knowing who is at greater risk for melanoma due to heredity, and understanding the pathways leading to cancer, are important steps in addressing a disease which is expected to be diagnosed in over 62,000 Americans in 2006," said National Institutes of Health Director Elias A. Zerhouni, M.D.

People with fair skin are generally at increased risk of developing melanoma. Differences in skin color, or pigmentation, are due largely to the melanocortin-1 receptor (MC1R) gene. Everyone has two copies of MC1R; one inherited from the mother and one from the father, and either can be the standard form or a variant. Some variant forms of MC1R are responsible for traits such as fair skin, freckling, and red hair. But MC1R may do much more than influence pigmentation.

"We previously observed that subjects who inherit one or two variant forms of the MC1R gene had a modest increase in risk of developing melanoma, even if they have

darker pigmentation," said Maria Teresa Landi, M.D., Ph.D., lead study investigator at NCI. "We have now discovered that MC1R dramatically predisposes individuals with no excessive sun exposure and variable pigmentation to developing a particular type of melanoma."

Melanomas, which are tumors that arise from cells which produce skin pigment, can occur on all parts of the body where these cells are present. Caucasians have a much higher chance than other populations of developing these tumors on skin areas that are exposed to the sun. Sun exposure has many effects on skin, including causing chronic sun damage, with wrinkling on areas subject to high exposure over a lifetime. Sun exposure may also lead to mutations in cancer-causing genes, such as BRAF, which are frequent in melanoma.

According to Boris Bastian, M.D., University of California, San Francisco, "The relationship between BRAF mutations in melanoma and sun exposure is complex and intriguing. On the one hand, sun exposure appears necessary for development of BRAF mutations; melanomas on areas such as the soles of feet and palms of hands, which have low exposure, have low mutation frequencies compared to the approximately 60 percent mutation frequency in sun-induced melanomas on skin without chronic sun damage. On the other hand, melanomas developing in older subjects with sufficient accumulated sun exposure to produce chronic damage also exhibit lower BRAF mutation frequencies."

Because melanomas on skin areas with few signs of chronic sun-induced damage occur in younger people and exhibit frequent mutations in BRAF, the researchers hypothesized that there were inherited genetic factor(s) that predispose to the development of these melanomas with BRAF mutations. An interesting candidate for this genetic risk factor was the MC1R gene.

To determine if there was an association between inherited variant forms of MC1R and the development of BRAF-mutant melanoma, the researchers studied the skin surrounding the melanomas in 85 patients from the Bufalini Hospital of Cesena, Italy, and 112 patients from the Department of Dermatology at the University of California, San Francisco, and identified subjects with no or little signs of chronic sun damage. They then sequenced MC1R genes in normal cells and BRAF in tumor cells and found that

BRAF mutations were more frequent in non-chronic sun-induced melanoma cases with hereditary genetic variant forms of MC1R.

By categorizing patients into two groups, those with no variant forms of MC1R versus those who had at least one variant, the scientists found that BRAF mutations were six to 13 times more frequent in those with at least one MC1R variant form. Looking more closely, the investigators found that the risk for melanoma with BRAF mutations rose with increasing number of MC1R variant forms. Comparing data from melanoma patients and healthy controls, the risk for melanomas with BRAF mutations increased from seven times for individuals with one MC1R variant form, to 17 times for those with two variant forms, when compared with individuals with the standard MC1R.

The study results show that normal variations in the MC1R gene in Caucasians have a very specific effect on melanoma susceptibility. Additional inherited factors that affect susceptibility may also be present, but they have yet to be discovered. "The mechanism by which variant forms of the MC1R gene facilitate development of melanomas with BRAF mutations is currently unknown," said Landi. "One possibility is that people with MC1R variant forms and variable pigmentation generate more reactive chemicals in their cells as a result of the ultraviolet exposure in sunlight. These reactive chemicals can induce mutations, like those in the BRAF gene, which may lead to cancer."

Clinical trials for melanoma using pharmaceutical drugs directed against the BRAF gene are ongoing. Knowledge of predisposing factors in the development of BRAF mutations, such as MC1R, might aid prevention and therapeutic strategies in the future.

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For more information about cancer, please visit the NCI Web site at http://www.cancer.gov, or call NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237).

*Landi MT, Bauer J, Pfeiffer RM, Elder DE, Hulley B, Minghetti P, Calista D, Kanetsky PA, Pinkel D, Bastian BC. *MCIR* Germline Variants Confer Risk for *BRAF*-Mutant Melanoma. *Science*, online edition, June 29, 2006.

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